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(21) International Application Number: PCT/NZ94/00084 (22) International Filing Date: 22 August 1994 (22.08.94) (30) Priority Data: 248486 24 August 1993 (24.08.93) NZ (71) Applicant (for all designated States except US): ASHMONT HOLDINGS LIMITED [NZ/NZ]; 48 Diana Drive, Glenfield, Auckland 1310 (NZ). (72) Inventor; and (75) Inventor/Applicant (for US only): HARVEY, Colin, Manson [NZ/NZ]; 44 Raymond Terrace, Birkenhead, Auckland 1310 (NZ). (74) Agents: PIPER, James, William et al.; James W. Piper & Co., 46 Brown Street, Ponsonby, Auckland 1002 (NZ).		(81) Designated States: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, ES, FI, GB, GE, HU, JP, KE, KG, KP, KR, KZ, LK, LT, LU, LV, MD, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SI, SK, TJ, TT, UA, US, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG), ARIPO patent (KE, MW, SD). Published <i>With international search report.</i>
(54) Title: ANTHELMINTIC FORMULATIONS (57) Abstract <p>This invention relates to anthelmintic compositions and has particular application to injectable compositions containing closantel together with an avermectin or milbemycin such as moxidectin, ivermectin, doramectin Milbemycin D, or other milbemycins together with a glycol based solvent such as polyethylene glycol or propylene glycol. The formulations may also include trace elements and/or vitamins.</p>		

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ANTHELMINTIC FORMULATIONS

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FIELD

This invention relates to veterinary compositions for the treatment of helminthiasis in warm-blooded animals, more particularly cattle, sheep, goats, and other domesticated herbivores.

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BACKGROUND

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Helminthiasis is a widely occurring disease in farmed animals. It commonly causes clinical disease and has significant adverse economic effects on farming economies when present at subclinical levels. Over the past twenty-five years a number of initially successful anthelmintic agents, with relatively specific effects on the metabolism of smaller or larger groups of endoparasites have been discovered, trialled, and used successfully to control helminthiasis on farms. Various groups of compounds have a greater or lesser spectrum of activity - that is to say they are able to destroy a wider or smaller range of parasite. For example, the widely used "ivermectin" is active against parasitic roundworms and also against some ectoparasites, yet it is inactive against tapeworms because of a difference in their biochemical constitution. "Triclabendazole" is active only against the liver fluke *Fasciola hepatica*.

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The drug closantel is a useful anthelmintic active agent that gives control over a range of internal parasites including liverfluke in cattle and sheep. For this reason it has been used in aqueous suspension in combination with other anthelmintics such as albendazole and mebendazole.

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This invention is based on the surprising discovery that an anthelmintic solution can be prepared from a combination of closantel and an avermectin or milbemycin like anthelmintic, for example ivermectin, moxidectin and doramectin. Such solutions have advantages in ease of use and may also be used by injection. Glycol based solvents such as polyethylene glycol and propylene glycol are able to dissolve both compounds to produce a stable formulation. Such formulations may also be dispersed in water.

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The milbemycins are described in the 11th Edition of the Merck index as a family of novel macrolide antibiotics with Milbemycin D in particular being used as an

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anthelmintic. The avermectins are described in the 11th Edition of the Merck index as a group of broad-spectrum antiparasitic compounds which are derivatives of pentacyclic 16-membered lactones related to the milbemycins. The most well known of these avermectins is ivermectin which is a semi-synthetic derivative of abamectin (one of the avermectins).

OBJECT

It is an object of this invention to provide novel veterinary compositions having anthelmintic activity.

STATEMENT OF INVENTION

In one aspect the invention comprises a composition including an effective amount of the anthelmintic closantel together with a glycol based solvent and an effective amount of at least one other anthelmintic.

In a further aspect the invention provides a method for treating helminthiasis in animals with compositions comprising an effective amount of the anthelmintic closantel together with a glycol based solvent and an effective amount of at least one other anthelmintic.

Preferably the other anthelmintic is chosen from the group comprising the avermectins or milbemycins. Such a group includes moxidectin, ivermectin, doramectin, Milbemycin D, as well as other milbemycins.

Preferably the compositions of the present invention are used by injection. They may also include trace elements and/or vitamins.

Preferably the closantel and other anthelmintic may be each present at from 0.5 to 15% w/v respectively, and more preferably the closantel is present at from 1 to 2% w/v.

In another aspect the invention provides a method of treating animals for helminthiasis by injecting a composition as previously described at the rate of 1mL/50kg of the animal's live weight (different dose rates and percentages of active ingredients will become apparent from the examples).

Preferably the closantel and other anthelmintic is dissolved in a mixture selected from

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at least two of: propylene glycol, polyethylene glycol, glycerol formal and water.

EXAMPLES

5 These and other aspects of the invention will be apparent from the following description, which is given by way of example only.

Example 1: % w/v

10	Closantel	3.75
	Ivermectin	0.08
	Propylene glycol to	100.00
	Polyethylene glycol	20.00

15 This formulation is suitable for use as an oral drench for sheep which would offer control of parasites resistant to older anthelmintics such as the benzimidazoles and levamisole as well as controlling adult liverfluke.

Example 2: % w/v

20	Closantel	3.75
	Moxidectin	0.10
	Propylene glycol	40.00
	Polyethylene glycol	20.00
	Water to	100.00

25 This formulation is suitable for use as an injection for sheep and cattle. It gives the advantage of longer action of moxidectin combined with activity against liverfluke.

Example 3: % w/v

30	Abamectin (88.8%)	1.13
	Sodium Closantel	1.30
	Glycerol formal (i)	40.00
	Water	30.00
	Sodium Selenate	1.20
	Tween 80	20.00
35	Benzyl Alcohol	1.00
	Glycerol formal (ii) to	100.00

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This is an injectable composition containing selenium.

Preparation Example

5 To a clean dry mixing vessel, add the glycerol formal (i) and Tween 80. With stirring, add the abamectin and sodium closantel, and heat to about 60° - 70° C with continued stirring until dissolved. Dissolve the sodium selenate in water and add to the batch while stirring. Allow to cool to room temperature and add the benzyl alcohol, stirring well to disperse. Make up to 100% volume with glycerol formal (ii).

10 Trial solutions of Example 3 were found to be stable overnight at 2°C, 21°C and 37°C with the active ingredients remaining soluble at all temperatures.

Use

15 This injectable formulation can be applied to cattle at a dose rate of 1mL/50kg of live weight, to provide the animal with 2.5mg/kg of closantel whilst at the same time supplying an effective dose of abamectin and a trace element such as selenium.

Example 4:

20	Dose rate	1ml/50kg
		g/L
	Abamectin	10
	Closantel	125
	Glycerol formal	400
25	PEG 400	600
	Benzyl alcohol	10

This provides another injectable formulation without the trace element by using a combination of polyethylene glycol (PEG 400) and glycerol formal.

30 Examples 5 - 7 show other injectable compositions containing different amounts of closantel to be used at a formulation dose rate of 1 mL/25kg of animal live weight.

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Example 5:

	Dose rate	1ml/25kg
5		g/L
	Abamectin	5
	Closantel	187.5
	Glycerol formal	400
	PEG 400	600
10	Benzyl alcohol	10

Example 6:

	Dose rate	1ml/25kg
15		g/L
	Abamectin	5
	Closantel	62.5
	Glycerol formal	400
	PEG 400	600
20	Benzyl alcohol	10

Example 7:

	Dose rate	1ml/25kg
25		g/L
	Abamectin	5
	Closantel	125
	Glycerol formal	400
	PEG 400	600
30	Benzyl alcohol	10

VARIATIONS

35 In addition to the combination of closantel and an avermectin or milbemycin the compositions of this invention can contain trace elements. Example 3 describes a composition containing selenium. Other trace elements or vitamins may be included.

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Examples of trace elements include copper, cobalt, iodine, zinc or the like. The vitamins may be for example vitamins A, B, D, or E.

5 ADVANTAGES

The compositions of this invention are stable and safe to use. The glycol based solvents used in this invention are non-irritant solvents and can safely be used in injectable compositions. The injectable compositions are particularly suited to the control of helminthiasis in cattle.

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CLAIMS

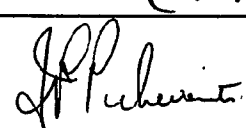
- 5 1. A composition including an effective amount of the anthelmintic closantel together with a glycol based solvent and an effective amount of at least one other anthelmintic.
2. A composition as claimed in claim 1 wherein the other anthelmintic is selected from the group comprising the avermectins and milbemycins.
- 10 3. A composition as claimed in claim 2 wherein the avermectins and milbemycins are selected from the group comprising abamectin, ivermectin, moxidectin, doramectin and Milbemycin D.
- 15 4. A composition as claimed in any one of claims 1-3 wherein the closantel and other anthelmintic is dissolved in a solvent selected from the group comprising: propylene glycol, polyethylene glycol, glycerol formal and water.
5. A composition as claimed in claim 4 wherein the closantel and other anthelmintic are each present at from 0.5 to 15% w/v respectively.
- 20 6. An injectable formulation comprising a composition as claimed in any one of claims 1-5.
7. An injectable formulation comprising a composition as claimed in claim 6 wherein the closantel is present at from 1 to 2% w/v.
- 25 8. A composition as claimed in any one of claims 1 to 7 wherein the closantel and other anthelmintic is dissolved in a mixture selected from at least two of: propylene glycol, polyethylene glycol, glycerol formal and water.
- 30 9. A method of treating animals for helminthiasis by injecting a composition as claimed in claim 7 at the rate of 1mL/25kg to 1mL/50kg of the animal's live weight.

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/NZ 94/00084

A. CLASSIFICATION OF SUBJECT MATTER Int. Cl. ⁵ A61K 31/16, 31/365 According to International Patent Classification (IPC) or to both national classification and IPC				
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) A61K 31/16 Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched AU: IPC as above Electronic data base consulted during the international search (name of data base, and where practicable, search terms used) DERWENT: Closantel or (Diodobenzamide and Antihelminth:) and A61K				
C. DOCUMENTS CONSIDERED TO BE RELEVANT				
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.		
A	AU,A,64533/90 (BANSTEAD ENTERPRISES LTD) 18 April 1991 (18.04.91)			
A	US,A,4470979 (VAN GESTEL) 11 September 1984 (11.09.84)			
A	Derwent Abstract Accession No. 94-014506/02 Class B05, SU,A,1782593, (IVAN AGRIC RES INST) 23 December 1992 (23.12.92).			
<div style="display: flex; justify-content: space-between; align-items: center;"> <div style="display: flex; align-items: center;"> <input type="checkbox"/> Further documents are listed in the continuation of Box C. </div> <div style="display: flex; align-items: center;"> <input checked="" type="checkbox"/> See patent family annex. </div> </div>				
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Date of the actual completion of the international search 17 November 1994 (17.11.94)		Date of mailing of the international search report 7 Dec 1994 (7.12.94)		
Name and mailing address of the ISA/AU AUSTRALIAN INDUSTRIAL PROPERTY ORGANISATION PO BOX 200 WODEN ACT 2606 AUSTRALIA Facsimile No. 06 2853929		Authorized officer  J P PULVIRENTI Telephone No. (06) 2832253		

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AU,A, 64533/90	EP 427582-A NZ 235647-A	ZA 9008165-A	US 5169846-A
US 4470979	CA 1217133-A		
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